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External beam radiotherapy in differentiated thyroid carcinoma: A systematic review

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ABSTRACT: External beam radiotherapy (EBRT) is not a first line treatment in differentiated thyroid carcinoma (DTC), but is recommended as an adjuvant treatment in certain cases. The evidence for EBRT in DTC is limited. A comprehensive literature search was performed. Data on patient demographics, disease stage, treatment characteristics, and outcomes were collected from included articles after quality appraisal. Sixteen articles met the inclusion criteria, with a pooled population of 5114. Only 1 study was prospective and there were no randomized controlled trials. Most of the evidence suggests that EBRT improves locoregional control in patients at high risk of locoregional recurrence. This was corroborated by analysis of pooled patient data. Available evidence suggests an improvement in locoregional control when EBRT is used in patients over the age of 45 at high risk for locoregional recurrence. However, there is a need for long-term prospective multicenter research on the subject. © 2015 Wiley Periodicals, Inc. *Head Neck* **00**: 000–000, 2015

KEY WORDS: radiotherapy, thyroid carcinoma, papillary thyroid carcinoma, follicular thyroid carcinoma, review

INTRODUCTION

Differentiated papillary and follicular thyroid carcinomata comprise at least 75% of thyroid cancers in the United Kingdom.[1] The treatment of differentiated thyroid carcinoma (DTC) depends on the stage and risk profile of the detected tumor, and includes hemithyroidectomy or total thyroidectomy with or without neck dissection and radioiodine treatment, followed by long-term thyroid-stimulating hormone suppression with thyroxine in medium and high risk patients.[2,3] Recurrence occurs in 10% to 15% of patients with DTC and is most frequently confined to the neck.[4]

The American Thyroid Association guidelines on DTC state that external beam radiotherapy (EBRT) "to treat the primary tumor should be considered in patients over age 45 with grossly visible extrathyroidal extension at the time of surgery and a high likelihood of microscopic residual disease, and for those patients with gross residual tumor in whom further surgery or RAI would likely be ineffective."[5] The British Thyroid Association guidelines recommend the use of EBRT in patients with gross evidence of local tumor invasion at the time of surgery with significant macroscopic residual disease, or in the case of residual or recurrent tumor failing to concentrate radioiodine.[6]

There are several factors contributing to the difficulty in studying the usefulness of EBRT in DTC. The indolent nature and low mortality rate of DTC mean large numbers and long follow-up are needed to produce statistically significant results. With ever-evolving cancer treatments, this means that patients enrolled in previous trials may have received different treatment to those enrolled more recently. Furthermore, EBRT is reserved for a relatively small subgroup of patients with significantly worse prognoses than the average patient with DTC.

Findings of published studies on the use of EBRT in DTC are not unanimous. Some authors found no statistically significant improvements in survival but recorded adverse effects of EBRT, thus refraining from recommending its use[7–9]; whereas others have shown impressive improvements in survival outcomes and locoregional control in the absence of major complications and recommend it in specific circumstances.[10–17] These studies were heterogeneous in their populations, methodologies, inclusion criteria, and outcome measures, making collation of evidence and application to clinical practice difficult.

There are no published systematic reviews or meta-analyses on the use of EBRT in DTC, and a search of the international Prospective Register of Systematic Reviews and the Database of Abstracts of Reviews and Effects yielded no results. This, together with the conflicting findings on EBRT in DTC, prompted this summary of existing evidence to better inform clinicians.

MATERIALS AND METHODS

Search strategy

Comprehensive searches were carried out independently by 2 reviewers (J.M.F. and R.C.) using Medline, CINAHL, EMBASE, and the Cochrane library databases.

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Search terms and Boolean operators used were "differentiated thyroid carcinoma" OR "thyroid neoplasms" OR "papillary carcinoma" OR "follicular carcinoma" AND "external beam radiotherapy" OR "radiotherapy" OR "intensity modulated radiotherapy." No date or language restrictions were applied. The final search was performed on October 15, 2014. Titles and abstracts were screened for relevance and relevant articles were obtained for assessment. Reference lists were manually searched for further relevant articles.

Eligibility criteria

All studies relating to EBRT use in DTC were considered. Only studies that included information on patient and tumor characteristics, treatment, and outcomes were included. Outcomes could be survival or locoregional control. Studies were excluded if they consisted of <10 subjects, or included patients with lymphoma, anaplastic carcinoma, or medullary carcinoma. Finally, studies that described the use of EBRT with palliative intent were excluded. This was defined by the use of EBRT alone and not as an adjunct to treatment with curative intent, or the use of EBRT to alleviate symptoms of advanced disease. Review articles were also excluded.

Data extraction

Data from included studies were collated using a proforma in Microsoft Excel (Redmond, WA). Article authors were contacted directly to obtain further information in cases of incomplete reported data.

Quality and risk of bias appraisal

All studies were assessed for quality and risk of bias by both reviewers, according to a modification of the system described in the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.[18] Because of the large number of retrospective, nonrandomized, nonblinded studies on the subject, more weight was placed on descriptions of interventions and reporting of outcomes than randomization and blinding.

Data analysis

Data extracted from the studies included in the quantitative review were analyzed using SPSS version 22 (IBM, Armonk, NY). Patient characteristics are presented as mean $\pm$ SE. Patient characteristics and differences in parameters between the treatment groups in the respective studies were examined using t tests for paired samples. Correlation was tested using the Pearson product-moment correlation coefficient. In all cases, a p value of $\leq .05$ was considered statistically significant.

RESULTS

Search results and study selection

This search strategy yielded a total of 821 articles. By screening the titles alone, 765 articles could be excluded, as they were either review articles, obviously not relating to the use of EBRT in DTC, or obviously not eligible for inclusion (for example, studies looking at EBRT for palliation of metastases). This left 56 abstracts, of which 6 were deemed by both reviewers to be ineligible for inclusion or irrelevant. Fifty full articles were then obtained for detailed assessment. Of these, 34 were excluded for a variety of reasons, including failure to meet eligibility criteria, high risk of bias, poor study design, or insufficient outcome data. This left 16 articles appropriate for inclusion in the review and 8 of these appropriate for quantitative analysis based on their comprehensive reporting of locoregional recurrence outcomes. All decisions to exclude studies were taken jointly by both reviewers. Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

Characteristics of included studies

The 16 studies selected for inclusion were published between 1993 and 2013 and originated from 9 different countries. Only 1 study was designed as a randomized controlled trial, and this was subsequently downgraded to a prospective cohort study because of low numbers of patients consenting to randomization.[8] This was the only multicenter trial. The other studies were comprised of 9 retrospective cohort studies and 6 retrospective reviews.

A total of 5114 subjects made up the study population from the 16 included studies. The average number of participants per study was 320 (range, 23–1297). Characteristics of the study population are detailed in Table 1. The overall male to female ratio was 1:3.1, and 89% of the tumors were papillary carcinomas.

Interventions

Interventions included surgery, EBRT, and radioiodine therapy in various combinations. This led to 6 possible treatment groups, as illustrated in Table 2. A total of 1442 patients were treated with EBRT with or without other treatment modalities. Intensity-modulated radiotherapy (IMRT) was used in 2 studies,[19,20] with the rest using standard EBRT. The anatomic area irradiated was described in 14 of the 16 studies; in the majority, this was the whole neck and upper mediastinum, with only 3 studies describing limited radiation fields focusing on the thyroid bed.[14,19] Durations of treatment ranging from 3 to 6 weeks were described, and the dose of radiation ranged from 38 to 72 Grays in 15 to 40 fractions.

Outcomes

Length of follow-up was variable among the studies, with a mean ranging from 2.5 to 9.9 years and median ranging from 3.2 to 11.3 years. These wide ranges were skewed by 4 low outliers with a mean of 2.5 years, and medians of 3.2, 3.5, and 4.6 years.[7,13,14,20] Together, these studies with <5-year average follow-up contained 596 subjects. A summary of the main findings of each study is illustrated in Table 3.

Locoregional control

Outcome reporting was variable between studies, of the 13 reporting overall locoregional recurrence rates; the mean rate of recurrence was 13.2% (range, 0% to 30.4%) of those treated with EBRT and 20.1% (range, 2.5% to 58.1%) of those not treated with EBRT. Several studies[8,10–14,16,17] showed statistically significant improvements

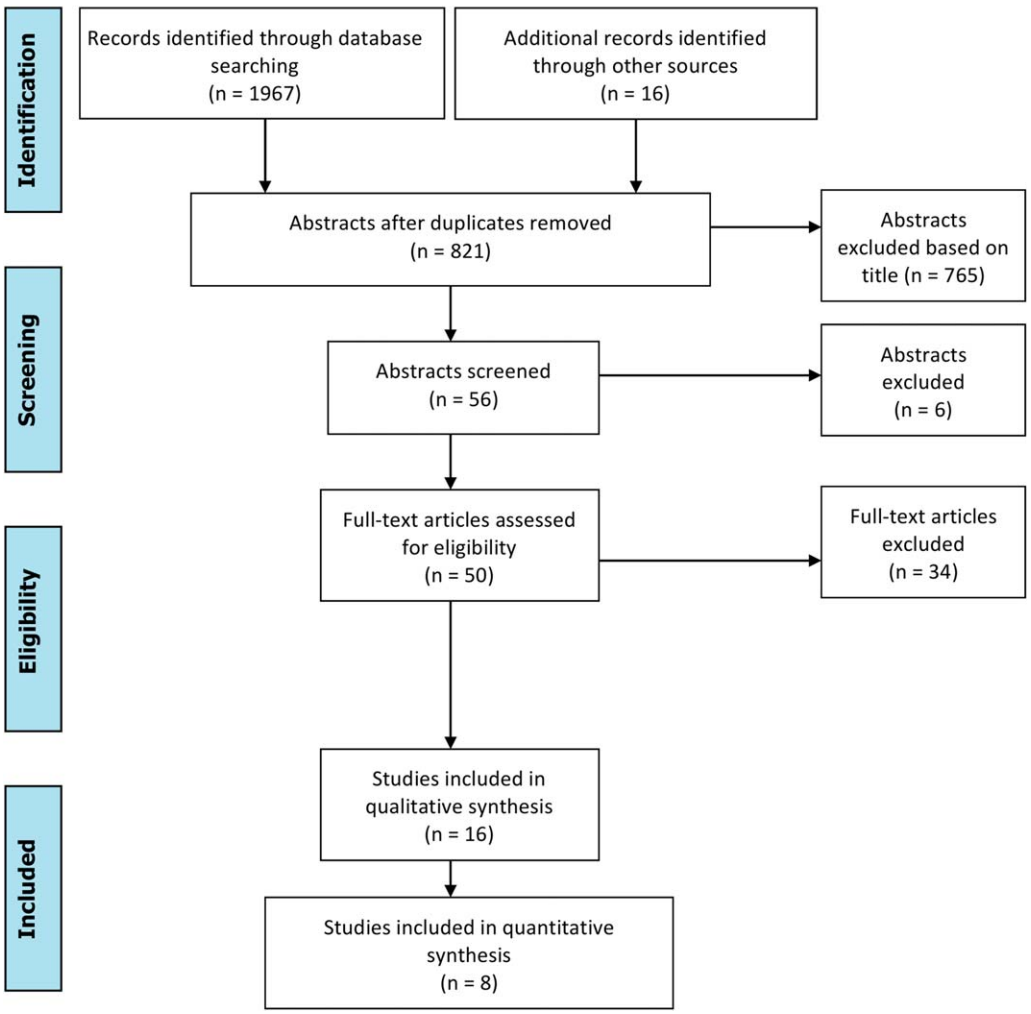

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 flow diagram. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

in locoregional control, particularly in higher risk subgroups. Chow et al[11] reported a large retrospective cohort study and found a statistically significant improvement in locoregional control in the subgroup of patients with macroscopic residual disease treated with EBRT compared with those not irradiated (10-year locoregional control rate 56.2% with EBRT vs 24% with no EBRT; relative risk = 0.36; $p < .001$). This study revealed a statistically significant reduction in the rate of distant metastasis after treatment with EBRT. The influential study by Brierley et al[10] demonstrated an improvement in locoregional control and statistically significant improvements in those patients receiving EBRT for papillary carcinoma who were over the age of 60, with microscopic residual disease, T4 disease, and no metastases (10-year locoregional relapse-free rate 86.4% with EBRT vs 65.7% with no EBRT; $p = .01$). Other studies reiterated significantly improved locoregional control in similar subgroups with advanced local disease and/or postoperative residual disease,[8,12,13,16] but 2 large retrospective reviews failed to show any difference overall in locoregional control in patients who had received EBRT compared with those who had not.[8,9]

Survival

Survival outcomes were reported variably among the studies and, in general, follow-up was not long enough to demonstrate survival effects. Only 3 studies reported a statistically significant improvement in survival in patients treated with EBRT, and these were all found in subgroup or multivariate analysis rather than the main study population.[8,10,16] Brierley et al[10] reported a large retrospective cohort study, which demonstrated improved cause-specific survival (CSS) over a median follow-up of 11.3 years in patients > 60 years of age with microscopic residual disease, no gross residual disease, and no metastasis who received EBRT. They also showed improved CSS in patients >60 years with T4 disease and no gross

TABLE 1. Population characteristics for included studies

Study	Year	Country	No. of patients	Sex		Age, y		Type of DTC			TNM classification							
				M	F	Mean	Median	Papillary	Follicular	PD	T1	T2	T3	T4	N0	N1	M0	M1
Biermann et al[7]	2009	Germany, Austria, and Switzerland	351	88	263	48	*	316	35	0	0	0	76	275	*	137	351	0
Tsang et al[8]	1996	Canada	382	100	282	47.2	*	262	120	105	*	*	*	*	223	155	328	39
Lin et al[9]	1997	Taiwan	699	*	*	*	*	574	125	0	*	*	*	*	*	*	*	*
Brierley et al[10]	2005	Canada	729	190	539	47	47	556	173	0	66	444	215	369	442	283	647	67
Chow et al[11]	2002	China	842	153	689	45.1	*	842	0	*	130	273	34	332	549	280	815	27
Keum et al[12]	2006	South Korea	68	23	45	*	57	68	0	0	0	0	0	68	11	57	68	0
Kim et al[13]	2003	South Korea	91	19	72	*	44	91	0	0	*	*	*	73	30	61	89	2
Kim et al[14]	2010	South Korea	23	4	19	*	64	19	0	4	*	*	3	17	3	20	18	5
Philips et al[15]	1993	Belgium	94	33	61	47	*	*	*	*	5	27	23	19	45	44	87	7
Chow et al[16]	2006	China	1297	245	1052	45.6	*	1297	0	0	444	180	412	185	855	420	1238	59
Farahati et al[17]	1996	Germany	169	43	126	*	*	125	44	0	0	0	0	169	98	71	169	0
Kwon et al[19]	2013	Korea	39	15	24	*	49	34	5	0	2	3	21	10	14	24	39	0
Schwartz et al[20]	2008	USA	131	75	56	*	57	104	21	*	0	5	11	109	29	95	94	37
Chen et al[21]	2009	USA	44	16	28	49.25	*	34	10	0	*	*	*	*	*	*	*	*
Meadows et al[22]	2006	USA	42	24	18	*	58.4	28	14	0	3	1	*	35	*	*	33	9
O'Connell et al[23]	1994	UK	113	43	70	53	*	85	24	*	6	24	13	53	59	54	101	12

Abbreviations: DTC, differentiated thyroid carcinoma; PD, poorly differentiated.
* Data not available.

TABLE 2. Intervention treatment groups

Study	Year	No. of patients	Total no. receiving EBRT	Treatment groups					
				Surgery + EBRT	Surgery + EBRT + RAI	Surgery + RAI	Surgery alone	EBRT alone	EBRT + RAI
Biermann et al[7]	2009	351	26	0	26	325	0	0	0
Tsang et al[8]	1996	382	185	51	123	92	97	6	0
Lin et al[9]	1997	699	72	72	*	*	*	*	*
Brierley et al[10]	2005	729	318	*	*	*	*	*	*
Chow et al[11]	2002	842	105	*	*	*	*	*	*
Keum et al[12]	2006	68	25	24	1	13	30	0	0
Kim et al[13]	2003	91	23	11	12	68	0	0	0
Kim et al[14]	2010	23	23	4	19	0	0	0	0
Philips et al[15]	1993	94	38	0	38	56	0	0	0
Chow et al[16]	2006	1297	192	28	163	817	289	0	0
Farahati et al[17]	1996	169	99		99	70	0	0	0
Kwon et al[19]	2013	39	39	36	3	*	*	*	*
Schwartz et al[20]	2008	131	131	12	119	0	0	0	0
Chen et al[21]	2009	44	11	3	8	33	0	0	0
Meadows et al[22]	2006	42	42	22	14	0	0	5	1
O'Connell et al[23]	1994	113	113	56	74	0	0	0	0

Abbreviations: EBRT, external beam radiotherapy; RAI, radioactive iodine treatment.
* Data not available.

residual disease after surgery who were treated with EBRT. Tsang et al[8] also reported an improved CSS in a subgroup of patients with papillary carcinoma and postoperative microscopic residuum (100% 10-year CSS vs 95% without EBRT; $p = .038$). Chow et al[16] demonstrated improved 10-year CSS (from 49.7% to 74.1%; $p = .01$) in patients with gross locoregional residual disease from their cohort study of 1297 patients. Although not statistically significant, Kwon et al[19] reported a cohort of patients who all received EBRT plus surgery for DTC of varying stages. They showed an overall survival rate of 97% with a median follow-up duration of 73 months, which compared favorably with previously reported cohorts of patients not treated with EBRT, who were likely to have less advanced DTC.

Adverse effects

There were 16 reports of grade 3 to 4 EBRT complications, which included 1 patient who required a tracheostomy for chronic laryngeal edema,[7] 2 patients with severe dysphagia,[14,15] and 13 patients with acute tracheitis or esophagitis requiring hospital admission.[8] In addition, Schwartz et al[20] reported 10 patients who suffered adverse effects after EBRT of a cohort of 131 patients, but did not include the grade of complication. Eight of these were related to esophageal stricture, and 2 were related to laryngeal edema and subglottic stenosis. They reported a significantly lower complication rate with IMRT as opposed to standard EBRT (2% vs 12%).

Quality assessment

Both reviewers assessed each trial against 13 criteria, including sample size, follow-up period, study design, clarity of description of aims, recruitment, inclusion and exclusion criteria, intervention, and outcomes. The average quality assessment score was 13 of 26 (range, 9–18). This was felt to be acceptable, as the nature of most of the studies precluded them from scoring for prospective design, randomization, and blinding. All except 1 study were single center, retrospective studies with potential for significant bias. There was significant clinical and methodological heterogeneity among the studies because of varying inclusion criteria, interventions, and outcome reporting.

Quantitative analysis

Eight studies were deemed suitable for quantitative analysis because of their ability to fulfil the eligibility criteria, inclusion and comparison of EBRT and non-EBRT treatment cohorts, and comprehensive reporting of locoregional control outcomes.[7,10–15,17,21] These comprised 2388 patients with a male to female ratio of 1:3.2 and an average age of 47.3 years. The primary tumor was T1 or T2 in 36.3% of patients and T3 or T4 in 67.7%, and there was regional nodal involvement in 44.3%, and distant metastasis in only 4.4%. Extracapsular extension of the primary tumor was noted in 58.9% of cases across the 8 studies, regardless of the treatment prescribed.

There was significant variation in treatment approaches between studies. The vast majority of patients underwent complete or subtotal thyroidectomy with or without neck dissection, followed by radioiodine therapy, EBRT, or both. Overall, 645 patients received EBRT and 1743 did not. Unfortunately, 2 studies did not report the number of patients who received EBRT and radioiodine therapy in combination.[10,11] After excluding these studies, only 16.1% of the patients who received EBRT did not also receive radioiodine therapy. It was not felt that these patients should be excluded from this review, as the reason for prescribing EBRT but not radioiodine therapy was poor tumor uptake of iodine in all cases. It was assumed that this was determined by postoperative radionuclide studies, although this is only explicitly stated in 1 study.[13] Radiation doses ranged from 45 to 70 Gray over variable

TABLE 3. Main outcome findings

Study	Population	Follow-up, y		Main outcome findings	
		Mean	Medium	Locoregional control	Survival
Biermann et al[7]	Multicenter prospective cohort study of 351 patients with locally invasive DTC.	2.5		Weak benefit of EBRT on local control (0% recurrence in EBRT group vs 3% non-EBRT) but not statistically significant. One significant toxicity, therefore, routine EBRT not recommended.	*
Tsang et al[8]	Single center retrospective review of 382 patients with DTC (1958–1985).	10.8		Statistically significant improvement in locoregional control in those with PTC and microscopic postoperative residuum who were treated with EBRT.	Statistically significant improvement in CSS in those with PTC and microscopic postoperative residuum who were treated with EBRT.
Lin et al[9]	Single center retrospective cohort study of all cases of DTC 1977–1994 (699 patients).			*	EBRT does not improve survival of patients with DTC – not recommended prophylactically – although may temporarily facilitate tumor regression.
Brierley et al[10]	Single center retrospective review of all patients with newly diagnosed DTC 1958–1998 (729 patients).		11.3	EBRT improves local control in specific groups at high risk: patients with papillary carcinoma and microscopic residual disease; age >60 y and T4 disease with no gross residual disease (10-y locoregional recurrence-free rate 86.4% vs 65.7%; $p = .01$).	EBRT improves CSS in specific groups at high risk, patients with papillary carcinoma and microscopic residual disease; age >60 y and T4 disease with no gross residual disease (10-y CSS 81% vs 64.6%; $p = .04$).
Chow et al[11]	Single center retrospective review of 842 patients with papillary carcinoma 1960–1997.		9.2	On multivariate analysis: EBRT recommended only for patients with postoperative residual disease to improve locoregional control (relative risk of locoregional relapse with EBRT 0.36; $p < .001$).	*
Keum et al[12]	Single center retrospective cohort study of 68 patients with papillary carcinoma invading the trachea 1986–1997.	8.5	8	Adjuvant EBRT effective in locally advanced DTC with tracheal invasion who have undergone shave excision of tracheal cartilage when microscopic/gross residual disease present (locoregional recurrence in 8% with EBRT vs 51% no EBRT; $p < .01$).	*
Kim et al[13]	Single center retrospective cohort study of 91 patients 1981–1997.		4.64	EBRT gives significantly better locoregional control at 5 y (EBRT 95.2% vs 67.5%; $p = .0408$) in patients with T4 tumors, residual tissue, or positive lymph nodes.	No difference in overall survival.
Kim et al[14]	Single center retrospective cohort study of 23 patients with locoregionally advanced/recurrent nonanaplastic thyroid carcinoma 2004–2008.		3.45	Comparison of 2 strategies for EBRT: recommend extended field EBRT because of improved locoregional control at 5 y ($p = .041$).	*
Philips et al[15]	Single center retrospective cohort study of 94 patients with DTC 1974–1989.		5.5	Supports use of adjuvant EBRT for locally advanced DTC with extrathyroidal spread/incomplete resection. Improves local control. Not statistically significant because of small numbers.	No difference in overall survival.

TABLE 3. *Continued*

Study	Population	Follow-up, y		Main outcome findings	
		Mean	Medium	Locoregional control	Survival
Chow et al[16]	Single center retrospective cohort study of 1297 patients with papillary carcinoma 1960–2000.	9.9		Overall EBRT improves local failure-free survival: relative risk of locoregional failure if no EBRT = 2.9 ($p < .001$). On multivariate analysis: EBRT indicated if gross locoregional residual disease/T4 tumor/positive resection margin/ nodal disease N1b or node > 2 cm – all led to statistically significant improvements in locoregional control.	On multivariate analysis: EBRT improved 10-y CSS in postoperative gross locoregional residual disease from 49.7% to 74.1% ($p = .01$).
Farahati et al[17]	Single center retrospective cohort study of 169 patients with DTC stage pT4 M0 1979–1992.			Statistically significant improvement in locoregional recurrence from adjuvant EBRT ($p = .004$) particularly in patients > 40 y ($p = .0009$), with invasive DTC with nodal involvement at presentation ($p = .01$).	*
Kwon et al[19]	Single center retrospective review of all patients with newly diagnosed DTC (M0) 1981–2010 (39 patients).		6.08	Adjuvant EBRT gives comparable locoregional control rate to historical controls with surgery alone, even though a larger proportion was at an advanced stage.	*
Schwartz et al[20]	Single center retrospective review of 131 with DTC (1996–2005).		3.2	EBRT showed a trend for improved locoregional control even in high-risk patients but only if disease surgically reduced to microscopic level. Not statistically significant.	EBRT showed a trend for improved overall survival even in high-risk patients but only if disease surgically reduced to microscopic level. Not statistically significant.
Chen et al[21]	Single center retrospective cohort study of 44 patients with DTC all with extracapsular extension after surgery.	7.8		Nonsignificant improved local recurrence rate with EBRT.	No difference in overall survival.
Meadows et al[22]	Single center retrospective review of 42 patients receiving EBRT for locally advanced/recurrent DTC 1962–2003.	6.9	4.1	Recommend EBRT after gross resection for patients aged >45 y with positive surgical margins, extrathyroidal extension +/or extracapsular nodal disease. Also recommend EBRT after surgery after locoregional recurrent disease in patients aged >45 y.	*
O'Connell et al[23]	Single center retrospective review of 113 patients with DTC 1969–1991.			Report rates of locoregional control and regression comparable with similar studies. EBRT should be considered in inoperable disease for and in those who fail to concentrate RAI.	*

Abbreviations: DTC, differentiated thyroid carcinoma; EBRT, external beam radiotherapy; PTC, papillary thyroid carcinoma; CSS, cause-specific survival; RAI, radioactive iodine.
* No outcomes reported.

periods of time, but radiation treatment was not described in detail.

Where possible, data on the EBRT and no-EBRT groups in each study were collected and locoregional control in the 2 groups was compared. There was no statistically significant difference in sex or nodal involvement between the 2 groups. Unfortunately, the studies on the whole did not report the T classification breakdown of those who received EBRT and those who did not, although one could reasonably assume that those who did receive EBRT had mainly T3 and T4 disease. This is likely to confound analysis of survival and recurrence in the 2 groups. Nevertheless, the mean recurrence rate in the pooled patients receiving EBRT regardless of stage or residual disease status was 8%, and in those who did not receive EBRT it was 25%, a statistically significant difference ($p = .0313$).

DISCUSSION

This review highlights the lack of good evidence for the use of EBRT in DTC. Furthermore, it is clear that there is wide variation in how it is used around the world. Although there is no consensus in the published literature on the indications for EBRT in DTC, most available evidence suggests improved locoregional control in certain patients. This is supported by quantitative analysis of reported overall locoregional control rates, which show a large statistically significant difference in favor of those who received EBRT.

Lack of statistically significant differences in survival outcomes is not surprising, considering the relatively small number of cases but also the indolent nature and favorable prognosis of most DTC cases. A large retrospective analysis showed a 98.6% cancer-specific survival rate among patients with DTC.[24] Such a survival rate requires very large numbers to show any statistically significant improvement. With advances in modern imaging technology, DTC is being diagnosed at an earlier stage, and fewer patients are candidates for EBRT. This highlights the importance of conducting multicenter studies with large numbers.

The reduced rate of locoregional recurrence in patients who received EBRT, reported in most of the studies, is particularly interesting given the poorer prognosis of those for whom EBRT is generally prescribed. Some studies report a statistically significant improvement in locoregional control in the overall cohort of patients who received EBRT as well as matched subgroups with similar risk factors, such as T4 disease and age.[10,11]

Importantly, the 2 studies that failed to show an improvement in locoregional control with EBRT were older studies.[8,9] The improvement in modern radiotherapy technology and techniques may account for the better outcomes in more recent studies. It is only in the last 10 to 15 years that IMRT has become readily available, as it relies upon precise 3D imaging technology and computer-controlled IMRT beams during treatment.[25,26] Now widely used, this form of treatment delivers better sparing, thus allowing refinement of clinical target volume. Treatment regimes and the dose-response relationship in IMRT are likely to improve treatment outcomes in the future.

Radioiodine therapy is the first line adjuvant treatment for DTC because of its high specificity for tumor tissue and favorable side effect profile. However, a small proportion of DTC is resistant or refractory to radioiodine therapy.[27] This group may benefit from EBRT. The adverse effects of EBRT in the head and neck are well documented and, although mostly mild, life-threatening cases, such as spinal cord necrosis, have been reported in patients with thyroid carcinoma.[28] Possible long-term effects, such as second primary malignancy, could not be assessed because of insufficient follow-up. For these reasons as well as the favorable prognosis of DTC in younger patients,[24] most authors only recommend EBRT in patients with DTC older than 45 years.

CONCLUSION

Despite the heterogeneous populations, varied inclusion criteria, and retrospective designs of the studies considered in this review, they do provide useful information to the clinician treating DTC. There are large numbers of patients from the pooled study cohorts and the evidence from recent studies suggests an improvement in locoregional control when EBRT is used in patients at high risk for locoregional recurrence and over the age of 45. Further long-term multicenter prospective research is needed, although the findings of this review suggest that EBRT is an adjuvant treatment modality that should be considered in such patients.

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